UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,084	03/07/2002	Clarence Webster Andrews III	PU3517USW	7283

23347 7590 02/17/2004

DAVID J LEVY, CORPORATE INTELLECTUAL PROPERTY
GLAXOSMITHKLINE
FIVE MOORE DR., PO BOX 13398
RESEARCH TRIANGLE PARK, NC 27709-3398

EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 02/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,084	ANDREWS ET AL.	
	Examiner	Art Unit	
	Deepak R Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-7,9-30,34-36 and 38-55* is/are pending in the application.

4a) Of the above claim(s) *15,16,21 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *2-7,9-14,17-20,23-30,34-36 and 38-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *30102 & 12203*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 2-7, 9-30, 34-36 and 38-55 are pending in this application.

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 11102003 is acknowledged. The traversal is on the ground(s) that the restriction requirement is improper. This is not found persuasive because this application is a national stage application under 35 U.S.C. 371 and lacks unity of invention under PCT Rule 13.2 which states that the applicants are entitled to a compound, a process of preparation of the compound, a composition, and a method of use. The compounds of formula (I) are drawn to patentably independent and distinct inventions as previously pointed out in office action dated October 22, 1996. In case of a single claim defining alternatives ("Markush Practice"), "the requirement of a technical interrelationship and the same or corresponding special technical features as defined in Rule 13.2, shall be considered to be met when the alternatives are of a similar nature". See MPEP, Appendix AI, Annex B. In the instant case, the alternatives defined for R^1, R^3, R^4, etc. are not art recognized equivalents and different issues of patentability may arise.

Applicant suggested modification to the restriction requirement (i.e., four-way restriction is replaced by the three groups listed in page 28) is considered favorably and is found to be acceptable. Group I (claims 2-7, 9-14, 17-20, 23-**30, 34**-36 and 38-55) drawn to compounds of formula (I) is considered as the elected invention.

The requirement is still deemed proper and is therefore made FINAL.

Claims 15-16 and 21-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11102003. Further, claim 15 (in part) drawn to 'compound of formula (ID) wherein R^3 and R^4 together with the nitrogen to which they are attached form a heterocycle', which falls within the invention of Group II (according to the modified restriction suggested by the applicant) is also withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being nonelected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 27-30 and 48-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of infection by HIV by inhibition of HIV reverse transcriptase, does not reasonably provide enablement for treatment of all other viral infections and/or prevention of infection by HIV. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the

art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The scope of the claims is not adequately enabled solely based on the activity related to HIV-1 reverse transcriptase inhibitory activity provided in the specification. First, the instant claims cover diseases due to viral infections that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The use disclosed in the specification is as pharmaceutical therapeutic agents having HIV-1 reverse transcriptase inhibitory activity, useful to treat all types of viral infections, which include AIDS, etc. Test procedures and assays are provided in the specification at pages 391-396 and IC50 values for some of the exemplified compounds are provided in Table 1, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of all types of viral infections embraced the instant claims. One of ordinary skill would not know to extrapolate this test data to compounds having the assorted types of substituents provided in the instant claims. The disorders encompassed by the instant claims include AIDS, etc., some of which have been proven to be extremely difficult to treat. There is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

The claims specifically recite 'treatment of a viral infection', however, there is no common mechanism by which all conditions due to viral infections arise. There are more than 400 distinct viruses that infect humans producing a wide range of diseases. Cecil Textbook of

Medicine states that "for many viral infections, no specific therapy exists. Proper use of antivirals requires specific viral diagnosis" (see the enclosed article, page 1742).

The list of diseases to be treated by the instant compounds includes HIV infection, which is known to be treated by antiretroviral protease inhibitors. However, the state of the art is indicative of the problems associated with such treatments and their efficacy. See Suarez et al. (PubMed Abstract enclosed), "Viral resistance, and pharmacokinetic problems, however, have limited the efficacy of these schemes". Also, Van Heeswijk (PubMed Abstract enclosed) regarding 'critical issues in therapeutic drug monitoring of antiretroviral drugs', expressed that "there are still many questions to be answered".

The instant claims 30, 52 and 54 recite '**preventing** HIV infection' which is not remotely enabled. Based on the HIV-1 RT inhibitory activity, the instant compounds are disclosed to be useful in the "prevention" HIV infection, for which applicants provide no competent evidence. "To prevent" actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Websters II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the 'preventive' effect. It is inconceivable how the *in vitro* activity of the representative compounds can be correlated to the 'prevention' of the disorder, such that the claimed compounds can not only treat but also "prevent" the disease associated with the stated activity. Further, there is no evidence on record which demonstrates that the *in vitro* screening test relied upon is recognized in the art as being reasonably predictive of success in any of the contemplated areas of 'prevention'. Such a reasonable correlation is necessary to demonstrate such utilities. See *Ex parte Stevens*, 16 USPQ 2d 1379 (BPAI 1990); *Ex parte*

Busse et al., 1 USPQ 2d 1908 (BPAI 1986) (the evidence must be accepted as "showing" such utility, and not "warranting further study").

State of the art references of record regarding the therapeutic approach of HIV infections provide several uncertainties. See De Clercq (cited in IDS) which states that "How long the treatment should be continued, and whether it could be discontinued or adjusted at certain time points, remain unsettled issues" (see page 38). Also, Balzarini (cited in IDS) provides that "Consequently, it is important to realize that the existing armamentarium of drugs and treatment modalities is clearly not sufficient to keep long-term control of the virus replication" (see page 18).

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

2. Claims 2-7, 9-14, 17-20, 23-30, 34-36 and 38-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compound or a pharmaceutically acceptable salt thereof, does not reasonably provide enablement for the entire scope of the recitation "pharmaceutically acceptable derivative". The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant claims recite "A compound ... or a pharmaceutically acceptable **derivative** thereof" wherein there is insufficient description in the specification regarding the types of derivatives intended by the recitation. The specification on page 29, lines 20-30, the term 'pharmaceutically acceptable derivative' is defined as "pharmaceutically acceptable salt, ester, salt of an ester or other derivative of a compound .... or an inhibitorily active metabolite ...", which is extremely broad. For example, the specification does not provide what 'ester' or 'other derivatives' of the compounds of formula (I) are intended because the instant structural formula already includes ester functional groups (see e.g., $-C(O)OR^{11}$, etc.). There is no disclosure regarding any other ester or other derivatives of compounds of formula (I). Similarly, the term "metabolite" is not sufficiently described. A metabolite is any compound which is pharmaceutically active *in vivo* when it undergoes 'metabolic' process and the specification does not provide any disclosure of what these compounds might be that *in vivo* transform in to the instantly claimed compounds.

It is suggested that the recitation "pharmaceutically acceptable derivative" be replaced with -- pharmaceutically acceptable salt -- in all occurrences (i.e., in claims 2, 5-7, 9, 11-13, 17-20, 23-25, and 38-42).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-7, 9-14, 17-20, 23-30, 34-36 and 38-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a. In claim 2, when R^4 is heterocycle, among the substituent list, the term "-$SR^{10}N(R^{10})_2$" is not understood. It is not clear whether the $-N(R^{10})_2$ is attached to the 'alkyl' group of R^{10} or directly to S, in which case the sulfur atom becomes trivalent and therefore requires a counter ion which has not been defined for the compounds. The discrepancy is also observed in claim 12 (see page 8, line 8).

b. In claim 2, when R^4 is aryl, in the list of substituents, the term "-$NC(O)R^{11}$" has the nitrogen with an open valency. It is not clear what is intended to be substituted on the nitrogen. The discrepancy is also observed in other claims, see e.g,, claim 6 (see page 5, line 1); claim 10 (page 7, line 3), etc.

c. Claim 3 recites the limitation "-$NS(O)_2R^7$" in line 5 as a substituent on the aryl group under the definition of R^4. There is insufficient antecedent basis for this limitation in claim 2 on which claim 3 is dependent.

d. In claim 3, line 5, the term "-$NS(O)_2R^7$" has the nitrogen with an open valency. The discrepancy is also observed in other claims, see e.g., claim 5 (see line 6); claim 6 (see line 21); claim 10 (page 7, line 1); etc.

e. In claim 4, there is no definition provided for the substituent R^5.

f. In claim 5, there is no definition provided for X.

g. In claim 6, X is defined to be "C, O or N" wherein the carbon and the nitrogen have open valencies. It is not clear what other substituents are intended to satisfy the

open valency. The discrepancy is also observed in other claims, see e.g., claim 10 (see line 4).

h. In claim 10, under the substituent list on aryl group of R^4, the term "-$OR^{11}OR^{11}$" (see page 7, line 2) is not understood. The list already consists of "-OR^{11}" (see the term immediately before the above term in question on line 2 of page 7). The discrepancy is also observed in claim 17.

i. Claim 24 provides many 'compound numbers' without any names or structural representation. A claim can not be complete without providing all details of the compounds claimed.

j. Claims 43-47 recite 'alkyl, **in particular** methyl' which is indefinite because a species has been recited within the claimed genus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 17 is rejected under 35 U.S.C. 102(b) as being anticipated by Wyatt et al. (J. Med. Chem. 1995). The instant claim reads on reference disclosed compounds, see the compounds disclosed in Table 1.

Claim 17 is rejected under 35 U.S.C. 102(b) as being anticipated by Brandl et al. (CAPLUS Abstract 76 :158266, 1972). The instant claim reads on reference disclosed compound, see the compounds disclosed in the abstract.

Claim 17 is rejected under 35 U.S.C. 102(b) as being anticipated by Perron et al. (CAOLD Abstract 55:5470f, 1960). The instant claim reads on reference disclosed compound, see the compounds disclosed in the abstract.

Receipt is acknowledged of the Information Disclosure Statement filed on March 1, 2002 and January 22, 2003.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (571) 272-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Deepak Rao
Primary Examiner
Art Unit 1624

February 9, 2004